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Allergic Disorders and Pregnancy

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The major conditions that the allergist-immunologist diagnoses and treats can occur in the context of gestation or in anticipation of pregnancy. Examples include asthma, allergic and nonallergic rhinitis, acute or chronic rhinosinusitis, nasal polyposis, urticaria, angioedema, anaphylaxis, and immunodeficiency. Goals of managing gravidas should include effective control of the underlying allergic-immunologic conditions, avoidance measures, guidance on medications, action plans or preparedness for emergencies such as acute severe asthma or anaphylaxis, and communication between the physician managing the allergic-immunologic conditions and the physician managing the pregnancy.

Asthma

Asthma occurs in 3.7% to 8.4% of pregnancies in the United States (1–3) and in up to 12.4% of pregnancies in Australia (4). Asthma may have its onset during gestation and present as acute severe asthma, requiring hospitalization. Wheezing dyspnea may result in interrupted sleep, persistent coughing, hypoxemia, and even rib fractures during gestation. The sequelae of ineffectively controlled asthma on the gravida can be devastating in that maternal deaths may occur in the most extreme cases (5, 6). Other untoward outcomes of asthma during gestation include fetal loss (abortions or stillbirths), increased rate of preterm deliveries (<37 weeks' gestation), intrauterine growth retardation (<2400 g), antepartum and postpartum hemorrhage, gestational hypertension, pre-eclampsia, oligohydramnios, and hyperemesis gravidarum (1,2, 5, 7,8–10, 11–12,13–17). Not all studies report all the listed complications. There is a troubling report of acute exacerbations of asthma during the first trimester being associated with an increased risk of congenital malformations (18). Repeated episodes of acute severe asthma during gestation have resulted in hypoxemic effects on the fetus. There is a report of pregnancy termination because of life-threatening acute severe asthma (19). Conversely, with cooperation between the gravida and physician managing the asthma and effective asthma control, there can be successful outcomes for most women (8–10, 11,13–17,20–22). Prevention of acute severe asthma has been associated with pregnancy outcomes approaching that of the general population (9). Use of inhaled cortiocosteroids (1,2,9, 11,14,20,22,23) has been effective as has prednisone in managing even the most severe cases of asthma during gestation. Some studies have reported small (100 g to 200 g) reductions in birth weight in gravidas who had used prednisone. Other studies have found essentially normal outcomes despite administration of prednisone as long as there was avoidance of hospitalizations and emergency care (9, 11).

Exacerbations of asthma during gestation may result in more hospitalizations than in nonpregnant patients with asthma. One mechanistic explanation is that there is reduced respiratory reserve in gravidas with asthma. It is also possible that they may receive less

comparison was made of emergency department treatment, 51 gravidas were compared with 500 nonpregnant women with asthma (24). Presentation peak expiratory flow rate (PEFR) was comparable (51% versus 53%) (24). However, corticosteroids were administered to 44% of gravidas compared with 66% of nonpregnant women (24). Hospitalization rates were similar (24% versus 21%). Unexpectedly, on discharge, oral corticosteroids were prescribed for 38% of gravidas and 64% of nonpregnant women (24). At the 2-week follow-up by telephone, asthma symptoms were reported by 35% of gravidas compared with 23% of nonpregnant women (24). Thus, pharmacotherapy was inadequate, in that oral corticosteroids were less likely to be prescribed with continued asthma symptoms at 2 weeks after emergency treatment. The 2008 American College of Obstetrics-Gynecology Practice Bulletin (2) and the National Asthma Education and Prevention Program Expert Panel Report (1,23) advise oral corticosteroids for treatment of acute episodes of asthma as part of a step-wise approach.

Physiologic Changes During Gestation

Although the frequency of respiration is not changed, tidal volume increases in pregnancy (25, 26). The minute ventilation rises 19% to 50% by late pregnancy (25– 27). Vital capacity is unchanged, unless there is an exacerbation of asthma. Oxygen consumption increases by 20% to 32%. Large increases in progesterone and estrogen produce a respiratory alkalosis from greater minute ventilation attributable to increased carotid body sensitivity to hypoxia (28). These changes occur before there is significant enlargement of the uterus. Arterial blood gas concentrations reflect a compensated respiratory alkalosis with pH ranging from 7.40 to 7.47 and partial pressure of carbon dioxide (P_{CO2}) from 25 mm Hg to 32 mm Hg (29, 30). The maternal partial pressure of oxygen (P_{O2}) ranges from 91 to as high as 106 mm Hg (30). The near-term alveolar-arterial oxygen gradient is 14 mm Hg in the sitting position compared with 20 mm Hg in the supine position. An explanation for the larger alveolar-arterial oxygen gradient when supine is decreased cardiac output because the enlarging uterus compresses the inferior vena cava which reduces venous return. In the third trimester, gravidas should try to avoid sleeping supine (29).

Total lung capacity is unchanged or reduced by 4% to 6%. The gravida breathes at reduced lung volumes because her residual volume and functional residual capacity are decreased. The diaphragm moves cephalad (27). As with the development of maternal hyperventilation, the residual volume and functional residual capacity decline before significant uterine enlargement occurs. The diaphragm flattens during gestation, and there is less negative intrathoracic pressure reported in some studies. One could speculate that early airway closure would occur if there were less negative intrathoracic pressure. Because during episodes of acute asthma, the gravida with asthma generates large negative intrathoracic pressures to apply radial bronchodilating traction, any decline in ability to develop more negative inspiratory pressures would predispose gravidas with asthma to more sudden deterioration because of airway closure.

Bronchial responsiveness to methacholine does not change in a clinically important way; however, a statistically significant change has been reported with PC20 increasing from 0.35 to 0.72 mg/mL from pre-conception to postpartum (31). In this study of gravidas

with mild asthma, the forced expiratory volume in 1 second (FEV_1) improved by 150 mL and the FEV_1 increased from 82% to 87% (31). The increase in serum progesterone concentration during gestation did not correlate with improvement in bronchial responsiveness (32). Although progesterone relaxes smooth muscles of the uterus and gastrointestinal tract, these findings suggest that factors other than progesterone contribute to changes in bronchial responsiveness.

Other Physiologic Changes

Cardiac output increases by 25% at 6 weeks and in later pregnancy can rise 30% to 60% because of the increase in heart rate and reduced vascular resistance (30,33,34). The latter results from estrogen supported generation of nitric oxide (35). The decrease in systemic vascular resistance is accompanied by an increase in the heart rate from 10 to 20 beats/minute. Stroke volume increases little; the uterine blood flow rises as much as 10-fold, from 50 mL/min to 500 mL/min at term (30). The blood volume increases an average of 1600 mL, and gravidas appear vasodilated as total body water expands by 1 L to 5 L (30,33,34, 36). Gravidas are sensitive to overzealous fluid administration. Although correcting any dehydration is indicated, injudicious fluid replacement has resulted in acute pulmonary edema with normal cardiac function. During the latter half of gestation, these changes become manifest because the gravida has increased pre-load (mild volume overload with activation of the renin-angiotensin-aldosterone system), increased chronotropy, and reduced afterload (30,33,34).

Even though during gestation there is a 20% to 40% increase in erythrocyte mass, the maternal hemoglobin concentration decreases (28, 30). The increase in erythrocyte mass is offset by the even larger increase of plasma volume resulting in relative anemia.

Fetal Oxygenation

The vascular resistance of uterine vessels (progesterone effect) declines so that there can be the large increase

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in uterine blood flow (30,34). The fetus survives in a low-oxygen environment with little reserve oxygen store, should the supply of oxygen-rich uterine blood be compromised. Animal and human studies demonstrate reduced fetal oxygenation if there is reduced uterine blood flow that may occur with severe maternal hypotension, hypocarbia, or shock (30). Maternal hyperventilation can reduce venous return and shift the maternal oxyhemoglobin dissociation curve to the left. Modest declines in maternal oxygenation seem to be tolerated satisfactorily by the fetus, but substantial degrees of maternal hypoxemia may threaten survival of the fetus. Uterine vessels during gestation are dilated maximally based on experimental data, primarily from pregnant sheep and from some human studies. Uterine vessels do not vasodilate after β-adrenergic agonist stimulation, but do vasoconstrict from α-adrenergic agonists. Some obstetric anesthesiologists administer ephedrine 25 mg to 50 mg intravenously if hypotension occurs during epidural anesthesia. The β-adrenergic effects of ephedrine result in increased cardiac output, which increases systolic blood pressure and maintains uterine perfusion. Intramuscular epinephrine provides primarily β-adrenergic stimulation, whereas intravenous epinephrine results in mostly β and some α effects.

The fetal hemoglobin is 16.5 g/L and the oxygen pressure at which hemoglobin is 50%

saturated is 22 mm Hg in the fetus, in contrast to 26 mm Hg to 28 mm Hg in the gravida (30, 37). Fetal umbilical venous P_{O2} measurements at term average about 32 mm Hg, with P_{CO2} 49 mm Hg. There is a very large shunt effect of the uteroplacental circulation; this is demonstrated when the gravida inspires 100% oxygen in the absence of acute asthma, fetal umbilical venous P_{O2} increases to 40 mm Hg and P_{CO2} is 48 mm Hg (37). Such changes in P_{O2} can be quite important for the fetus in distress, although the uteroplacental shunt is large. For the same incremental increases in arterial P_{O2}, the leftward shift of the fetal hemoglobin oxygen dissociation curve results in larger increases in fetal oxygen saturation than in maternal blood.

In summary, fetal oxygen delivery depends on many factors, but most critical are blood flow (maternal cardiac output) to the uterus, integrity of the placenta, and maternal arterial oxygen content.

Effects of Pregnancy on Asthma

For the individual gravida, it is not always possible to predict the effects of pregnancy on asthma. Studies in the literature report varying degrees of improvement, deterioration, or no change in the clinical course (2,38). Over the past 3 decades, the published reports appear to be rather consistent, with approximately equal proportions of patients being unchanged, improving, or deteriorating. In a review from 1980 of nine studies involving 1,059 pregnancies, 49% of gravidas were unchanged in terms of severity of asthma, 29% improved, and 22% worsened (39). A prospective study of 198 pregnancies in 1988 recorded somewhat similar results in that 40% of gravidas had no change in medications, 18% of gravidas required fewer medications, but 42% required more medications (40). Similarly, using medication and symptom diary cards, during 366 gestations in 330 gravidas with mild or moderate asthma, asthma was unchanged in 33%, improved in 28%, and worsened in 35% (41). In a prospective study of 873 gravidas with asthma from 2003, 44% had no symptoms or treatment during the pregnancy, 32% had intermittent asthma, and 23% were considered to have persistent asthma (mild 13%, moderated 7%, and severe 4%) (13). How effective is the asthma control? In a series of 2,123 gravidas with asthma, about 33% had acute “unscheduled” care ranging from office visits to hospitalizations (42). It is not known if ineffectively controlled asthma contributed, but there is a report of an association between maternal asthma and intellectual disability in children (43). The association also was increased in the presence of maternal diabetes, renal or urinary tract conditions, and epilepsy (43).

Pregnancy in adolescents with asthma has been associated with many emergency department visits and hospitalizations for asthma (44). Some adolescents with severe asthma may not benefit from the prescription of anti-inflammatory medications because of poor adherence (45). The combination of poverty, inadequate or no prenatal care, limited education, and not being able to make control of asthma a priority can complicate pregnancies at any age of the gravida but especially during adolescent pregnancies.

Cigarette smoking during gestation can have long-term effects. Maternal smoking of 20 or more cigarettes/day *in utero* was associated with current asthma in 14-year-old girls but not in 14-year-old boys (46). These findings support the persistence of harmful effects of smoking *in utero* even if the gravida then quits after she delivers. Adverse effects on the child's lung function, FEV_1 and FEF_{25-75} and FEV_1/FVC, have been demonstrated in 7- to 18-year-olds whose mothers smoked during pregnancy or where another member (but

not the gravida) smoked during the pregnancy (47). Clearly, gravidas must not smoke during gestation for their own well-being and that of their children.

Choice of Therapy

The approach to therapy includes making an assessment of the level of control, severity, and risks (1,2,23,48,49) (Table 39.1). Specifically, it should be determined (a) whether the gravida has near fatal (potentially fatal) asthma (48,49), (b) whether allergens in the home or workplace are contributing, and

(c) whether the gravida is likely to be adherent to the recommendations provided.

Table 39.1 Goals of Therapy for Management of the Gravida with Asthma

- • Prevent maternal fatalities and fetal demise
- • Maximize asthma control
- • Prevent hospitalizations, emergency department visits, and unscheduled care visits
- • Prevent/reduce nocturnal asthma
- • Prevent/reduce limitations of activities, school or work absenteeism/presenteeism
- • Maximize respiratory status and pulmonary function
- • Use appropriate medications
- • Prepare an Action Plan for exacerbations

Avoidance Measures

General avoidance measures include cessation of smoking and preferably recommending

that there be no second-hand smoking in the home environment. There should be no or very minimal consumption of alcoholic beverages, cessation of illicit drug use, and avoidance of drugs with teratogenic or harmful potential. Examples of these include tetracyclines (discoloration of infant's teeth from insufficient production of enamel), sulfonamides in the last trimester (glucose-6 phosphate dehydrogenase G6PD deficiency could cause hemolytic anemia), troleandomycin, clarithromcyin, methotrexate, mycophenolate mofetil, and antibiotics such as quinolones.

When there is allergic asthma, individual avoidance measures should be implemented for animals, dust mites, cockroaches, and fungi. Aspirin and nonsteroidal anti-inflammatory drugs should be withheld in the gravidas with aspirin exacerbated respiratory disease. However, nonselective anti-inflammatory drugs such as ibuprofen or naproxen (50) are considered appropriate for the first 32 weeks of gestation, if indicated for aspirin-tolerant gravidas. Acetaminophen is acceptable.

Medications

There are increasing data to justify the appropriate use of many medications for treatment of asthma and its comorbidities during gestation (Table 39.2) (1,2,13,14,16,21,23,50–53). Where feasible, it is preferable to use inhaled as opposed to oral medications; to some extent this point has become moot in that there are data to justify appropriate use of oral medications. In human gestation, organogenesis is proportionately relatively short (days 12 to 56) compared with animals. Drugs are infrequent causes of major congenital malformations, which have an overall rate of 3% to 7% depending on the studies and degree of ascertainment (54). About two-thirds of malformations are from unknown factors and an additional 25% are genetically determined. About 5% of malformations have been associated with environmental factors including medications, maternal infections, and radiation.

Table 39.2 Appropriate Medications during Gestation

- **Anti-asthma Medications**
  - Albuterol, levalbuterol
  - Salmeterol
  - Formoterol
  - Budesonide, beclomethasone dipropionate, fluticasone
  - Prednisone/methylprednisolone
  - Cromolyn
  - Montelukast/Zafirlukast
  - Nedocromil
  - Theophylline
  - Epinephrine (intramuscular)

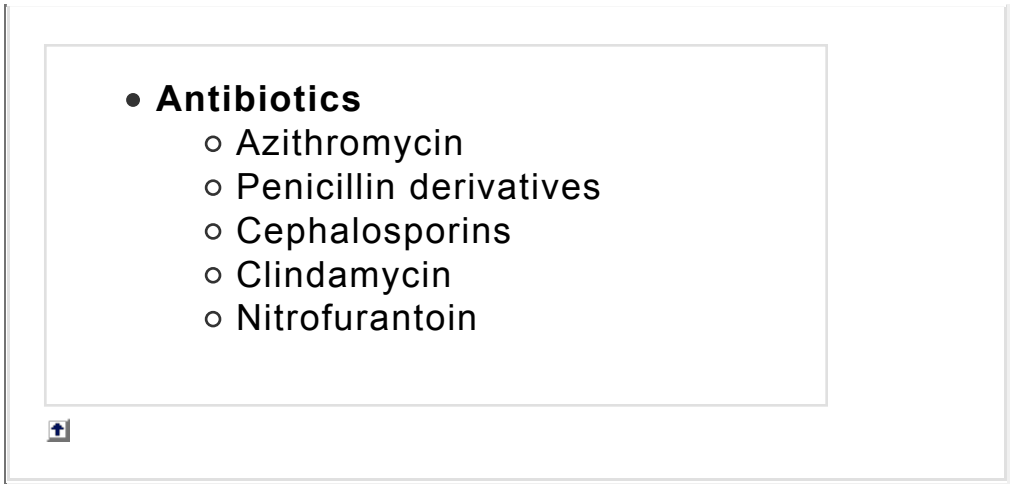
- Terbutaline
- Ipratropium bromide

- **Allergen Immunotherapy**

- **Tri-Valent Inactivated Influenza Vaccine**

- **Anti-rhinitis Medications**
  - Budesonide, beclomethasone dipropionate, fluticasone
  - Cromolyn
  - Loratadine
  - Cetirizine
  - Levocetirizine
  - Diphenhydramine
  - Chlorpheniramine
  - Pseudoephedrine (third trimester only, if at all)

- **Gastroesophageal Reflux Disease Medications**
  - Lansoprazole
  - Esopmeprazole
  - Rabeprozole
  - cimetidine
  - Ranitidine
  - Famotidine



Examples of teratogenic agents include ethanol, isotretinoin, phenytoin, carbamazepine, valproic acid,

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angiotensin-converting enzyme inhibitors, diethylstilbestrol (vaginal carcinoma), thalidomide, inorganic iodides, lithium carbonate, tetracycline, doxycycline, streptomycin, mycophenolate mofetil, and some antineoplastic drugs that have not caused fetal loss earlier. Erythromycin has been associated with an increase in cardiac malformations, and clarithromycin has a U.S. Food and Drug Administration (FDA) category C rating (50).

Most to almost all medications for use for asthma are considered appropriate for treatment in pregnancy. The strength of this statement varies depending on the first trimester data (1,2,13,14,18,20,21,23,50–53). There is only a single citation and limited experience with use of formoterol (51); there is more experience with salmeterol (23,53). Harm has not been described. The combination product of budesonide/formoterol has been used effectively as reliever and controller therapy in nonpregnant women (55). It is an FDA category C drug in the United States. It may well be an acceptable therapy during gestation as a reliever medication as data are accumulated.

Human data on the use of oral corticosteroids have not identified teratogenic effects for prednisone, methylprednisolone, or hydrocortisone, and they are recommended when indicated (1,2,9, 11,22,23,53). The most published data for inhaled corticosteroids report on belcomethasone dipropionate and budesonide. Most gravidas with mild persistent and some with moderate persistent asthma will be managed effectively with budesonide or other inhaled corticosteroids such as beclomethasone dipropionate. The American College of Obstetricians and Gynecologists Practice Bulletin (2) concluded that “budesonide is the preferred inhaled cortiocosteroid for use in pregnancy.” The National Asthma Education and Prevention Program (NAEPP) Working Group took a view that “inhaled corticosteroids other than budesonide may be continued in patients who were well controlled by these agents prior to pregnancy especially if it was thought that changing formulations may jeopardize control”(1).

Oral steroids should be initiated early during exacerbations, as doubling of the inhaled corticosteroid from whatever was the controlling dosage often is ineffective unless the controlling dosage was “pediatric” such as budesonide 200 μg/day to 400 μg/day. In a study of nonpregnant patients who were managed with a mean dose of beclomethasone

dipropionate of 710 µg/day, the approach tried was that of doubling the inhaled corticosteroid when there were 15% or greater reductions of peak expiratory flow rates or increased symptoms (56). This approach did not prevent the need for oral corticosteroids, which were initiated when the peak expiratory flow rate decreased by 40% (56). Therefore, the gravida should be aware that the inhaled corticosteroid, inhaled corticosteroid/albuterol, or inhaled corticosteroid/long-acting β_2 agonist combination may be inadequate for some exacerbations of asthma. Although this statement applies to gravidas with severe persistent asthma, it also applies to gravidas with mild or moderate persistent asthma who might experience a severe worsening of asthma when there is an upper respiratory infection.

Cromolyn (53, 57) has a very long record of use for asthma (allergic rhinitis and allergic conjunctivitis) and can be recommended for intermittent or mild or moderate persistent asthma. It can be effective as prophylactic treatment before exercise, cold air and/or fume exposure, and for pet dander or mold exposures. Nedocromil (53) also inhibits early and late bronchial responses to allergens as does cromolyn and both are labeled FDA Category B.

Leukotriene antagonists, montelukast and zafirlukast, are designated as FDA Category B and are recommended (23) for moderate and persistent asthma as alternative treatments. It is informative that one series of 96 women did not identify an increased risk of teratogenicity (52).

Albuterol is recommended as the short acting β_2-adrenergic agonist of choice (2,23). The NAEPP Working Group advises that for acute exacerbations of asthma “up to 3 treatments of 2–4 puffs by MDI at 20 minute intervals or single nebulizer treatment” can be started at home (23). This author would suggest that albuterol be limited to 2 inhalations and prednisone 40 mg to 60 mg initiated instead of up to 12 inhalations in the first hour if there is no physician present. If the gravida remains quite dyspneic, she should seek emergency department or perhaps office assessment and care.

Some gravidas with severe asthma during pregnancy may require low to moderate dose prednisone administered on an alternate-day basis to maintain effective asthma control. Experience with alternate-day prednisone, along with intermittent courses of daily prednisone (40 mg to 60 mg each morning for 5 to 7 days) for exacerbations has resulted in avoidance of emergency department visits and hospitalizations and normal pregnancy outcomes such as newborn birth weight, head circumference, and length (9–10, 11).

Theophylline is not contraindicated for treatment of asthma during gestation, but has a narrow therapeutic index and is considered an alternative therapy (2). Its metabolism is altered by many factors, and drug interactions must be considered. The peak serum concentration should be in the range of 5 µg/mL to 12 µg/mL.

Allergen Immunotherapy

Allergen immunotherapy can be continued or even initiated during pregnancy. The only recognized risk from allergen immunotherapy is anaphylaxis. There are no data to suggest that women are more likely to experience anaphylaxis from allergen immunotherapy when pregnancy occurs. Data from 121 pregnancies in 90 gravidas receiving allergen immunotherapy showed a

low incidence of anaphylaxis (58). The Joint Task Force on Practice Parameters of the American Academy of Allergy, Asthma and Immunology (AAAAI); American College of Allergy, Asthma and Immunology (ACAAI); and Joint Council of Allergy, Asthma and Immunology advises that dosing of immunotherapy not be increased during pregnancy (59). This author believes that as long as the gravida is not having systemic reactions to immunotherapy, she can have the dosage increased in the normal manner. Indeed, the goal of immunotherapy is to reduce the symptoms and need for medications. Allergen immunotherapy does not protect the fetus from subsequent development of atopic disorders (58, 60).

Acute Asthma

As in managing the nonpregnant patient with asthma, exacerbations of asthma should be reversed as quickly and effectively as possible. Acute severe asthma (status asthmaticus) has been associated with intrauterine growth restriction (retardation), stillbirths, maternal deaths, and untoward effects on the fetus such as cerebral palsy from inadequate oxygenation. The goal in treating the gravida with acute asthma is to minimize maternal hypoxemia, hypocarbia, or respiratory acidosis and to maintain adequate oxygenation for the fetus.

β_2-adrenergic agonists (such as albuterol) are the drugs of choice for home or emergency department/hospital use (1,2,23). If the gravida presents in the emergency department and the initial response to albuterol is incomplete, oral or intravenous corticosteroids should be administered promptly. Continued acute severe dyspnea may necessitate continued nebulized therapy or additional albuterol by metered-dose inhaler. There must be monitoring of oxygen and overall respiratory status. Ipratropium may be administered with albuterol but is not the primary treatment. Some gravidas with very severe dyspnea will not respond to albuterol administered by nebulizer or metered-dose inhaler; in that setting, epinephrine can be administered intramuscularly as 0.3 mL (1:1000). The justification for epinephrine is as follows: (a) it is synthesized endogenously, (b) it is not teratogenic, (c) it is metabolized rapidly, (d) its onset of action is rapid, and (e) variables associated with drug delivery by inhalation do not have to be considered. The use of epinephrine for acute asthma or anaphylaxis increases cardiac output, which can maintain uterine perfusion in contrast to the fear that epinephrine will cause fetal loss by decreasing uterine blood flow. The adverse effects of acute severe asthma (or anaphylaxis) can be a serious threat to the gravida or fetus.

The NAEPP Expert Panel Report suggested that home treatment of the acute exacerbation could include inhaled β_2-adrenergic agonist (albuterol) therapy from 2 to 4 inhalations every 20 minutes in the first hour or as a single nebulizer treatment (23). With a good response defined as peak expiratory flow >80% of the personal best, no wheezing or shortness of breath, a response to the albuterol treatment lasting for 4 hours and no apparent drop in fetal kick counts, the gravida should continue the albuterol and double the inhaled corticosteroid for the next 7 to 10 days (23). If the gravida has an incomplete response, such as having continued wheezing and shortness of breath and the peak expiratory flow rate being 50% to 80%, an oral corticosteroid was recommended. A poor response to the initial treatment was defined as peak expiratory flow of <50%, marked wheezing and shortness of breath, and decreased fetal kick activity. The gravida, in that

case, should begin the oral corticosteroid, repeat the albuterol, call for medical advice and proceed to the emergency department (23).

A personalized approach uses the level of asthma severity to guide therapy. How much medication and what types have been used in the past to control the asthma? How responsive has the asthma been? Have there been previous hospitalizations, intensive care unit admissions, or intubations? The latter two events imply a diagnosis of potentially (near) fatal asthma (48,49). If there was poor adherence in the past, it can be anticipated that guideline-type of control will not be achievable. Alternative treatment plans should be considered.

When the gravida presents with moderate or severe acute wheezing dyspnea, oral corticosteroids should be administered with the initial albuterol or albuterol/ipratropium treatment. For example, prednisone 40 mg to 60 mg is an appropriate dosage. The initial beneficial effects may be in 2 to 6 hours or longer. If the initial treatment is not effective over the first 2 hours, it is likely that acute severe asthma (status asthmaticus) has occurred. Hospitalization or treatment in an observation unit is indicated; theophylline has not been found to be superior to albuterol and intravenous methylprednisolone therapy. In some gravidas with acute severe asthma, it may be sufficient to monitor the pulse oxygenation measurements. In other gravidas, an arterial blood gas determination will be necessary to monitor the P_{CO2} and pH. Some gravidas require fetal heart monitoring during or before discharge.

Excessive fluid replacement is not indicated, but volume depletion should be corrected. The gravida can develop acute pulmonary edema (noncardiac) from excessive crystalloid administration as she is volume-expanded during gestation. The resultant acute dyspnea may be attributed to acute severe asthma when it is from fluid overload and noncardiac pulmonary edema.

When the gravida, who has experienced an exacerbation of asthma, is discharged from the emergency department, observation unit, or hospital, a short course of oral corticosteroid should be administered to prevent continued symptoms and signs of asthma

(1,2,23,61). In the rare setting of acute respiratory failure during acute severe asthma, an emergency cesarean delivery may be necessary (19,62).

Persistent Asthma

Some types of persistent asthma during gestation are listed in Table 39.3. Should gravidas require daily medication, an allergy-immunology consultation is indicated to identify and address IgE-mediated triggers of asthma, to determine if allergic bronchopulmonary aspergillosis is present, and to provide expertise in the diagnosis and treatment of nasal polyps, cough, rhinitis, or rhinosinusitis. Avoidance measures are indicated to reduce bronchial hyperresponsiveness and the need for antiasthma medications.

Table 39.3 Classification of Asthma during Pregnancy

- • Intermittent
- • Persistent (allergic or nonallergic)
  - • Mild
  - • Moderate
  - • Severe
- • Potentially (near) fatal asthma
- • Asthma with allergic bronchopulmonary aspergillosis
- • Aspirin exacerbated respiratory disease (aspirin intolerant asthma)
- • Adolescent asthma

The goals of management include maintaining a functional respiratory status, as well as minimizing wheezing dyspnea, nocturnal asthma, exercise intolerance, emergency department visits, acute severe asthma, and maternal fatalities or loss of the fetus (Table 39.1).

Dyspnea can be sensed during gestation in the absence of asthma during the first two trimesters (63). A respiratory rate of more than 18 breaths/min has been considered a warning sign for pulmonary pathology complicating “dyspnea during pregnancy” (63). A comorbidity to consider includes peripartum cardiomyopathy.

Many gravidas can be managed effectively with inhaled budesonide or beclomethasone dipropionate and inhaled albuterol for symptomatic relief. For gravidas who have intermittent asthma or mild persistent asthma, inhaled budesonide or beclomethasone diproprionate, cromolyn, leukotriene-receptor antagonists, or possibly theophylline are appropriate during gestation. A short-acting bronchodilator such as albuterol would be recommended if needed. If these drugs are ineffective because of worsening asthma, such as from an upper respiratory infection, a short course of prednisone such as 40 mg

daily for 5 to 7 days may be administered. Antibiotics can be prescribed for secondary bacterial infections after viral upper respiratory infections, acute bronchitis, or exacerbations of chronic or subacute rhinosinusitis. Azithromycin, ampicillin, amoxicillin, amoxicillin-clavulanate, or cephalosporins are appropriate antibiotics (Table 39.2).

For severe persistent asthma, higher dosages of budesonide or other inhaled corticosteroids can be used as can fluticasone/salmeterol (23) or budesonide/formoterol. Higher doses of inhaled corticosteroids may produce systemic side effects. Proper inhalation technique is necessary and should be assessed periodically. Should asthma be managed ineffectively with avoidance measures and the inhaled corticosteroid/long-acting β_2-adrenergic agonist combination, then cromolyn, leukotriene-receptor antagonists, or theophylline can be considered (1,23).

If the gravida has significant wheezing on examination, nocturnal asthma, or major changes in spirometry or peak expiratory flow rates, a short course of prednisone may be indicated to relieve symptoms and improve respiratory status. If the gravida has improved after 1 week of prednisone, either the prednisone can be discontinued or it can be converted to alternate-day administration and tapered (9, 11). The most effective antiasthma medications for chronic administration during gestation in order of efficacy are prednisone, inhaled corticosteroids, and then inhaled β-adrenergic agonists (albuterol, levalbuterol, or terbutaline), leukotriene-receptor antagonists, cromolyn, and theophylline. Theophylline has a low therapeutic index and for the most part, is not considered anti-inflammatory. In some gravidas with severe persistent asthma, bronchiectasis from allergic bronchopulmonary aspergillosis, or inhaled corticosteroid phobia, theophylline can be used. It is not teratogenic in humans. Comorbidities such as allergic rhinitis, rhinosinusitis, and gastroesophageal reflux disease should be addressed (Table 39.2).

Essentially all patients can be managed successfully during gestation. Some patients with potentially (near) fatal asthma are unmanageable because of noncompliance with physician advice, medications, or in keeping ambulatory clinical appointments. Such gravidas are considered to have malignant potentially fatal asthma. Long-acting methylprednisolone (80 mg to 120 mg intramuscularly) is of value to prevent repeated episodes of status asthmaticus or respiratory failure. This approach should be instituted to try to prevent fetal loss or maternal death in the nearly impossible-to-manage gravida. Adequate documentation in the medical record is needed. Psychologic, psychiatric, and social work evaluations may be obtained. Gravidas with malignant potentially fatal asthma, however, may refuse evaluation or necessary therapy. The serum glucose should be determined regularly because of hyperglycemia produced by long-acting methylprednisolone. Other antiasthma medications should be minimized to simplify the medication regimen.

Labor and Delivery

When asthma is controlled effectively, the gravida can participate in prepared childbirth methods without limitation. Minute ventilation increases to as great as 20 L/min during labor and delivery (37). Should cesarean delivery be necessary, complications from anesthesia should not create difficulty if asthma is well controlled. When the gravida has used inhaled corticosteroids or oral corticosteroids during gestation, predelivery

corticosteroid coverage should include 100 mg hydrocortisone intravenously every 8 hours until postpartum, and other medications can be used. Parenteral corticosteroids suppress any asthma that might complicate anesthesia required for cesarean delivery. The prior use of recommended dosages of inhaled corticosteroids or alternate-day prednisone should not suppress the surge of adrenal corticosteroids associated with labor or during anesthesia.

When the gravida who requires regular moderate- to high-dose inhaled corticosteroids or daily or alternate-day prednisone plans to have a cesarean delivery, preoperative prednisone should be administered for 3 days before anesthesia. The gravida should be examined ideally 1 to 2 weeks before delivery to confirm stable respiratory status and satisfactory pulmonary function. In gravidas with persistent mild asthma, preanesthetic therapy can consist of 5 days of inhaled corticosteroid.

When the gravida presents in labor in respiratory distress, emergency measures such as inhaled albuterol and oral or intravenous corticosteroids should be administered promptly. Adequate oxygenation and fetal monitoring are essential.

Rhinitis During Pregnancy

Intranasal obstruction and nasal secretions can be very troublesome during gestation and interfere with sleep. It has been reported that 18% to 61% of gravidas experience symptoms of rhinitis during some time during gestation (64). Nasal congestion during gestation may be influenced by (a) increased blood volume, (b) progesterone's effects causing smooth muscle relaxation of nasal vessels, (c) estrogen's effects causing mucosal edema, (d) production of nitric oxide, which is a vasodilator, from the maxillary sinuses, and (e) effects of vasodilating neuropeptides.

Nasal biopsy results from symptom-free gravidas showed glandular hyperactivity manifested by swollen mitochondria and increased number of secretory granules (65). Special stains demonstrated increased metabolic activity, increased phagocytosis, and increased acid mucopolysaccharides, thought to be attributed to high concentrations of estrogen. Similar findings were present in gravidas with nasal symptoms. Additional findings included increased (a) goblet cell numbers in the nasal epithelium, (b) cholinergic nerve fibers around glands and vessels, and (c) vascularity and transfer of metabolites through cell membranes (65). Women who used older (stronger) oral contraceptives but in whom no nasal symptoms had occurred had similar histopathologic and histochemical changes, as did symptom-free gravidas (66). Regarding post-nasal drainage, it has been estimated that in nonpregnant females, 700 mL to 900 mL of nasal secretions are generated per day for proper conditioning of inspired air. In some gravidas, this volume may be even greater and secretions are not reabsorbed, which results in symptoms of rhinitis, post-nasal drip, or cough.

Nasal congestion causing symptoms is likely to occur in the second and third trimesters. However, it may occur in the first trimester as well (64). The differential diagnosis for rhinitis of pregnancy includes allergic rhinitis, nonallergic rhinitis (including nonallergic rhinitis with eosinophilia), nasal polyposis, and rhinosinusitis or purulent rhinitis resulting from enlarged inferior turbinates that are occlusive with the nasal septum. There can be referred pain to the sinuses consistent with rhinologic or contact headache, a condition that mimics an exacerbation of rhinosinusitis. Rhinitis medicamentosa may be present

when there has been excessive use of topical decongestants.

Treatment of nasal symptoms during gestation necessitates an accurate diagnosis, effective pharmacotherapy, and, in some cases, avoidance measures. For example, smoking and illicit drugs should be discontinued, as should topical decongestants. Intranasal budesonide or beclomethasone dipropionate are indicated to relieve nasal obstruction. There are published asthma data for budesonide and beclomethasone dipropionate; however, the very low bioavailability of other corticosteroids such as mometasone and fluticasone suggests that they also are appropriate during gestation. If large nasal polyps are present and topical corticosteroids are ineffective, a short course of prednisone should be prescribed. The blood glucose should be monitored because the gravida is prone to hyperglycemia.

Antihistamines help gravidas with milder degrees of allergic rhinitis and occasionally with some nonallergic types of rhinitis. As of 1977, there had been very long-term experience and safety for chlorpheniramine (1,070 exposures), diphenhydramine (595 exposures), and tripelennamine (121 exposures) (67). These first generation antihistamines remain appropriate (Table 39.2) but second generation antihistamines are acceptable and infrequently sedating. Loratadine was used in 2,147 pregnancies (68) and has the most published experience in pregnancy. By analogy, the metabolite of loratadine, desloratadine, should be appropriate as well. Cetirizine and its parent, hydroxyzine, were not associated with teratogenic effects in 39 and 53 pregnancies, respectively (69) or in 196 pregnancies, of which 153 women used cetirizine within 5 weeks of the last menstrual period (70). Data on cetirizine have shown that it

is not teratogenic (69,70). A very conservative approach is to avoid its use during the first trimester or in women planning a pregnancy.

For perspective, the FDA classification system category B means that animal studies are negative but that human studies have not been conducted or that animal studies are positive but such findings of fetal risk have not been demonstrated in human pregnancies. FDA category C implies that animal studies have identified adverse fetal effects and that there are no controlled studies in human pregnancies or human data aren't available (50,71). The proviso is to use such medications only if the “potential benefit outweighs the potential risk to the fetus” (50,71). The FDA category B medications include chlorpheniramine, loratadine, and cetirizine whereas fexofenadine and azelastine are FDA category C (71). The leukotriene-receptor antagonists, montelukast and zafirlukast, are category B (71) and experience in 96 pregnancies did not identify harm (52). Intranasal (or ocular or orally inhaled) cromolyn is considered appropriate (57) and is FDA category B. Except for budesonide, nasal corticosteroids remain FDA category C, although their benefits outweigh any risks.

This author tries not to prescribe pseudoephedrine to avoid potential α-adrenergic stimulation of uterine vessels, even though it has not been found to be teratogenic (71, 72). Phenylpropanolamine (not available in the United States) in 726 exposures was associated with significantly greater risk of malformations (ear and eye), whereas this risk was not detected with pseudoephedrine (39 exposures) or phenylephrine (1,249 exposures) (67).

Antibiotics for pregnant women with infectious rhinosinusitis or purulent rhinitis are listed

in Table 39.2. Ampicillin, amoxicillin, amoxicillin-clavulanate, azithromycin, and cephalosporins are initial antibiotics, depending on the prior therapy of the gravida. Sulfonamides are contraindicated because of the possibility of G6PD deficiency in the fetus. Tetracyclines are contraindicated because of maternal fatty liver during gestation (third trimester) and staining of teeth in the infant. Human experience with clarithromycin is not available, so azithromycin should be used if it is indicated. FDA category B antibiotics include azithromycin, cephalosporins, clindamycin, erythromycin, and penicillins, which include ampicillin/sulbactam and amoxicillin/clavulanic acid. (71). FDA category C antibiotics consist of aminoglycosides, chloramphenicol, clarithromycin, quinolones, sulfonamides, tetracycline derivatives, and vancomycin (71).

Allergen immunotherapy helps reduce the need for medications in cases of allergic rhinitis or asthma. This therapy can be continued in pregnancy and, if symptoms are severe and the gravida agrees, immunotherapy may be initiated during gestation. During immunotherapy in 121 pregnancies in 90 gravidas, 6 gravidas experienced anaphylaxis (58). No abortions or other adverse effects occurred (58). The decision to begin immunotherapy after delivery often is made for the purpose of convenience and ability of the woman to present for injections in a timely fashion. Severe allergic rhinitis symptoms during gestation can be treated with intranasal corticosteroids and antihistamines.

As stated earlier, the dose of allergen immunotherapy can be increased in the absence of large local reactions or systemic reactions. There is no evidence that the incidence of anaphylaxis from allergen immunotherapy (or skin testing) is greater during the time of gestation.

Replacement immunoglobulin for gravidas with primary or secondary immunodeficiency should be continued or initiated during gestation. The dosage is at least 0.4 g/kg every 4 weeks.

Urticaria, Angioedema, and Anaphylaxis

Urticaria or angioedema should be evaluated and treated during gestation with little change from the nongravid state, detailed in Chapter 31. Some causes for urticaria and angioedema include foods, medications, infections (viral), and underlying autoimmune conditions such as collagen vascular disorders. Some episodes of urticaria are attributable to dermatographism or other physical urticarias, chronic (autoimmune) urticaria, or idiopathic acute urticaria. The differential diagnosis during gestation includes hereditary angioedema (HAE) (73–74,75–77), pruritic urticarial papules and plaques of pregnancy (PUPPP) (78), herpes gestationis (79), and prurigo of pregnancy.

In the series of Frank et al. (74), there was an increased frequency of attacks of HAE in only 2 of 25 gestations. No acute episodes of HAE occurred during delivery. In contrast, Chappatte and deSwiet reported on the unpredictability of HAE during gestation and a maternal fatality (73). From a series of 227 pregnancies in 107 women in the PREHAEAT project of the European Union, HAE worsened in 38% of women, was unchanged in 32%, and was less severe in 30% (77). It was reported that the course of HAE was usually similar to the prepregnancy course (77). The concentration of C1 inhibitor declines in normal pregnancy because of increased plasma volume. Some gravidas have worsening clinical symptoms and create major management problems. Contraception is advisable as a rule. Stanozolol or danazol result in a fourfold to fivefold increase in the concentration

of C1 inhibitor and C4. Although stanozolol has been administered during gestation without masculinizing fetal effects or fetal loss (73), its use is discouraged in gravidas with HAE. Contraception should be used if a woman is receiving attenuated androgens for HAE. Genetic counseling is advisable for women with HAE because it is an autosomal-dominant condition, although there is incomplete penetration.

For acute severe central episodes of HAE, rapid administration of intramuscular epinephrine has been used, but additional specific therapy will have to include danazol 600 mg to 800 mg immediately or stanozolol, 4 mg four times a day, and airway care measures (intubation or tracheostomy). Fresh frozen plasma also may be infused on an emergent basis in some situations. Although unavailable in the United States, a concentrate of C1 inhibitor for parenteral administration has proved effective, with onset of action in 10 to 60 minutes (76). Antifibrinolytic agents are considered unwise to use in pregnancy because of their potential thrombotic effects. Nevertheless, three pregnancies in one gravida occurred uneventfully despite use of ε-amino-caproic acid (80).

During gestation, no specific maintenance therapy is necessary in gravidas with peripheral HAE. Based on Frank's series of gravidas with peripheral or central (upper airway involvement) HAE, exacerbations during the time of tissue trauma, delivery, did not occur (74). In the PREHAEAT project, there were exacerbations of HAE postpartum or within 48 hours of delivery in just 6% of pregnancies (77). If an episode of upper airway obstruction occurs during a cesarean delivery, epinephrine, danazol, stanozolol, and intubation would be indicated. Use of C1 inhibitor concentrates, if available and of low risk, otherwise would be of value acutely.

The PUPPP syndrome occurs in the last trimester and begins on the abdomen with numerous extremely pruritic, erythematous, urticarial plaques and papules surrounded by pale halos (78). Topical corticosteroids are of value, and maternal or fetal complications are unlikely. The plaques and papules may last until 6 weeks postpartum. Herpes gestationis consists of intense pruritus followed by lesions that may be bullous, papulovesicular, or pustular (79). Some gravidas develop tense grouped vesicles on the abdomen or extremity.

Pharmacologic treatment of chronic urticaria or angioedema often is required. The antihistamines listed in Table 39.2 are recommended. Prednisone may be indicated for acute exacerbations of urticaria, angioedema, or anaphylaxis. Leukotriene-receptor antagonists are appropriate but often do not provide relief for urticaria in nonpregnant women.

Anaphylaxis during gestation has been described after penicillin (81), cefotetan (82), Hymenoptera stings (83), oxytocin (84), diclofenac (85), phytomenadione (86), fentanyl (87), ferric gluconate (88), antisnakebite venom (89), latex (90), and succinylcholine (91). Anaphylaxis during gestation has caused fetal distress, fetal encephalopathy, or fetal demise. Gravidas have experienced profound shock with reduced uterine blood flow during anaphylaxis as the fundamental insult to the fetus. As in other cases of anaphylaxis, prevention and emergency medications and therapy are needed. Epinephrine intramuscularly should be administered promptly. If the gravida is hypotensive, then usual resuscitative measures should be instituted to maintain blood pressure and the airway. Obstetric assistance should be obtained immediately should

cesarean delivery be indicated.

Venom Immunotherapy

Venom immunotherapy is a highly efficacious form of therapy to prevent future episodes of Hymenoptera anaphylaxis. Graft (92) reported a successful pregnancy in a gravida treated with maintenance dosages of wasp and mixed vespid venoms. Subsequently the Committee on Insects of the AAAAI reported 63 pregnancies in 26 gravidas with no definite systemic reactions (93). Five of 43 gestations resulted in spontaneous abortions, thought to be unrelated to stings or immunotherapy. One term infant (2.7%) had multiple congenital cardiovascular malformations; this incidence is within the range of expected congenital malformations. The Joint Task Force on Practice Parameters of the AAAAI, ACAAI, and the Joint Council of Allergy, Asthma and Immunology suggested that the dosages of venom not be increased during pregnancy (59). This author would take a more aggressive approach and continue to build up during the injections in the absence of systemic reactions or large local reactions (>8 cm). Other issues should be discussed with the gravida, such as avoidance measures and personal use of epinephrine.

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